IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Hope, Ernest G.	Attorney Docket No.: HOPEP002
Application No.: 09/722,096	Examiner: Yaen, Chistopher H.
Filed: 11/22/2000	Group: 1643
Title: ANTI-ANGIOGENIC CELLULAR AGENT FOR CANCER THERAPY	Confirmation No.: 4236

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I hereby certify that this correspondence is being transmitted electronically through EFS-WEB to the Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450 on February 21, 2008.

Signed: /Swapnali Joshi/
Swapnali Joshi

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the attached sheets.

I am the attorney or agent acting under 37 CFR 1.34

Respectfully submitted,
BEYER WEAVER LLP

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Encl : Remarks in support of pre-appeal brief request for review

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Atty Docket No: **HOPEP002US**
Client Ref:

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Hope, Ernest G.

Application No: 09/722,096

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Title: ANTI-ANGIOGENIC AGENT FOR CANCER THERAPY

Examiner: Yaen, Chistopher H.

Art Unit: 1643

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REMARKS IN SUPPORT OF PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant respectfully requests pre-appeal brief review of the final rejections, under 35 U.S. C. § 102, over Lu and Negrin and over Alvernas. As the claims distinguish the two cited references for the same reasons, the arguments have been consolidated.

Claims 101-106, 108-110, 118-120, 122-128, 131-141, and 173-175 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lu and Negrin and also by Alveranas (hereafter "Lu/Alvernas"). Final Office Action, pages 2-3. The only pending independent claim, claim 101 recites:

> A composition comprising an ex vivo expanded population of cytotoxic lymphocytes having the ***ability to kill tumor-associated vasculature cells***, and a pharmaceutically acceptable carrier, wherein said population is ***produced by expanding lymphocytes in a closed system with agitation***, and said population has a cytotoxic activity characterized in that ***specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask***, as measured in a ^{51}Cr-release assay wherein the population is added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1.

Claim 101 recites a composition comprising a cell population that differs from Lu/Alvernas's population in terms of (1) culture conditions ("closed system with agitation"), (2) an

anti-tumor "cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1," and (3) "the ability to kill tumor-associated vasculature cells."

Lu/Alvernas's "cytokine-induced killer (CIK)" cells were grown in standing tissue culture flasks, i.e., open systems, without agitation, as was conventional for lymphocyte cultures in 1994. Growth in a "closed system with agitation" as recited in the pending claims yields a population that has a significantly higher anti-tumor cytotoxic activity than the Lu/Alvernas cells. This activity, a functional property, explicitly excludes Lu/Alvernas's CIK cells. It is well-settled that an invention may be defined by functional properties. *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430 (C.A.F.C. 1988).

The Examiner stated that "it can be argued that culturing the cell population by agitation, as claimed, only further purified what was already characterized by Lu *et al.*" Office Action dated February 8, 2007, page 3. This statement demonstrates the error in the rationale underlying the novelty rejection. Even if Applicant had done nothing more than "further purify" Lu/Alvernas's cell population, which Applicant does not concede, the resulting composition would be different from Lu/Alvernas's composition, in that it would be further purified. ***A purer composition is different from a less pure composition.*** If the claims recite a different composition than that described in a cited reference, ***the claims cannot properly be rejected for lack of novelty under 35 U.S.C. § 102 over that reference.*** The pending claims unquestionably recite a different composition than Lu/Alvernas's because the claims explicitly exclude Lu/Alvernas's composition.

The Examiner appears to suggest that two cultures starting with the same lymphocytes, but subjected to different culture conditions would not be expected to produce different cell populations. Nothing could be further from the truth. For example, different culture conditions often favor growth of one or more cell types in a heterogeneous population of cells and/or conversely result in reduced growth or loss of other cell types from the population. The presence or absence of different cell types in two cell populations represents a material, structural difference between those two cell populations. Even if the two cell populations were to contain exactly the same cell types, but in different proportions, the two cell populations would be different.

Moreover, culture conditions can affect the make-up of particular cells, as well as the make-up of a cell population. To illustrate this point, Applicant submited an abstract from Carswell, K.S. & Papoutsakis, E.T., *Biotechnicol. Bioeng.* (May 2000) 328-38 ("Exhibit A" accompanying the Amendment dated August 8, 2007). This abstract describes attempts to culture human T cells in stirred bioreactors for cellular immunotherapy applications. Notably, the authors reported that "[e]xposure to agitation and sparging . . . [caused] a significantly increased rate of downregulation of the interleukin-2 receptor (IL-2R). This finding illustrates that differences in the physical conditions of cultures can lead to clear structural differences, in this case, the amount of IL-2R on the cell surface in the presence of IL-2. As one skilled in the art knowns, such a change would also alter the properties of a cell population grown under such conditions. Specifically, greater downregulation of IL-2R would lead to a commensurate reduction in IL-2 responses mediated by that receptor.

In the present case, Applicant's specification contains side-by-side comparative evidence that growth in a closed system with agitation produced a composition with a different property than cells grown in standard flasks. In particular, as shown in Figure 2B, cells grown in a closed system with agitation show significantly higher specific lysis of OCI-Ly8 B-cell lymphoma cells, as measured in a ^{51}Cr-release assay when added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1. The closed system-grown cells had a 35% higher specific lysis of OCI-Ly8 B-cell lymphoma cells than cells grown in standard flasks. This is a material difference in the context of the invention, which was to prepare a population of cells suitable for immunotherapy. More specifically, a significant increase in cytotoxic activity of the cells allows the clinician to reduce the number of cells that need to be infused to treat a patient's cancer, which reduces the risk of stroke.

This difference in anti-tumor cytotoxic activity could not have been predicted, given that, before the priority date of the present application application, lymphocytes were not standardly grown in closed systems with agitation, and efforts to expand cytotoxic lymphocytes in bioreactors were not generally successful. Exhibit A, which was published between the priority date and filing date of the present application, evidences that, under the disclosed conditions, T cells and T cell lines either grew less well in with agitation and/or in bioreactors, were more fragile, or showed an increased rate of down-regulation of IL-2 receptor. If anything, these results would suggest that the activity of a cytotoxic T cell population grown in a closed system with agitation would be reduced, rather than increased, compared to standard flask-grown cells. Accordingly the requirement that "specific lysis of

OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask" recited in claim 101 represents an unexpected, as well as material, difference over the cited art.

Thus, claim 101 defines a population of cells that is produced by a materially different method and has a materially different anti-tumor activity. For this reason, claim 101 clearly distinguishes the Lu/Alvernas reference.

Claim 101 also distinguishes the Lu/Alvernas reference based on its recitation of "the ability to kill tumor-associated vasculature cells." The ability to kill tumor-associated vasculature cells, while sparing normal vasculature cells, had never previously been described for any population of cells. The Examiner's argument that this property was inherent in Lu/Alvernas's cells cannot properly be maintained, as claim 101, on its face, defines a population of cells that is materially different from Lu/Alvernas's. According to the M.P.E.P., a "prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." M.P.E.P. § 2112.01 (citing *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977)). Applicant has meet this burden by establishing that the claimed population is different from Lu/Alvernas's with respect to anti-tumor activity. As those of skill readily appreciate, once it is established that Lu/Alvernas's cells represented a different population than the claimed population, there is simply no credible scientific basis for assuming that Lu/Alvernas's cells ***necessarily*** had "the ability to kill tumor-associated vasculature cells," as recited in claim 101. It is well-settled that "[i]nherency . . . may not be established by probabilities or possibilities." *Continental Can Co. USA, Inc.* v. *Monsanto Co.,* 948 F.2d 1265, 1268-69 (Fed. Cir. 1991) (quoting *In re Oelrich,* 666 F.2d 578,581 (C.C.P.A. 1981)). For this additional reason, then, claim 101 is clearly patentable over Lu/Alvernas.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4160.

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